Answer 1:

Bibliographic Information

Impact of imatinib* on the pharmacokinetics and in vivo efficacy of etoposide and/or ifosfamide. Rezai, Keyvan; Lokiec, Francois; Grandjean, Isabelle; Weill, Sophie; de Cremoux, Patricia; Bordier, Vincent; Ekue, Richard; Garcia, Mickael; Poupon, Marie-France; Decaudin, Didier. Department of Pharmacology Oncology, Centre Rene Huguenin, Saint-Cloud, Fr. BMC Pharmacology (2007), 7 No pp. given. Publisher: BioMed Central Ltd., CODEN: BPMHBU ISSN: 1471-2210. http://www.biomedcentral.com/content/pdf/1471-2210-7-13.pdf Journal; Online Computer File written in English. CAN 148:229420 AN 2008:77247 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: Using a human small cell lung cancer (SCLC) xenografted in nude mice, we have previously reported enhanced tumor growth inhibition following chemotherapy in combination with imatinib (STI571). We therefore investigated the in vivo impact of imatinib on the pharmacokinetics and efficacy of chemotherapy. Methods: Two different human tumors were used: SCLC6 small cell lung cancer xenografted in nude mice, and LY-3 EBV-assocd. human B-cell lymphoma xenografted in SCID mice. Plasma, urine, and fecal concns. of etoposide (VP16) were detd. by a validated high performance liq. chromatog. method. Plasma concns. of ifosfamide were detd. by a validated gas chromatog. assay with nitrogen-phosphorus detection. Results: Slight tumor growth inhibition was induced by imatinib administered alone in one in vivo EBV-assocd. B-cell lymphomatous xenograft. In contrast, an increase of the chemotherapy-induced antitumor effect was obsd. in the lymphoma model but not in a small cell lung cancer model when mice bearing human xenografted tumors were treated concomitantly by imatinib and chemotherapy. This antitumor effect was not influenced by concomitant administration of fluconazole. The AUC0-3h (Area Under the concn.-time Curve) of etoposide was increased when mice were treated with etoposide + imatinib due to decreased fecal excretion. In contrast, imatinib did not appear to influence the urinary excretion of etoposide, and concomitant administration of the CYP3A4 inhibitor, fluconazole, with imatinib did not modify the pharmacokinetics of etoposide plus imatinib alone. Conclusions: Altogether, these results therefore justify further prospective phase I and II clin. trials with combinations of etoposide-based chemotherapy and imatinib in patients with certain cancers, such as malignant lymphoma, with careful toxicol. monitoring.

Answer 2:

Bibliographic Information

Clinical and mechanistic aspects of glucocorticoid-induced chemotherapy resistance in the majority of solid tumors. Zhang, Chengwen; Wenger, Till; Mattern, Juergen; Ilea, Septimia; Frey, Christian; Gutwein, Paul; Altevogt, Peter; Bodenmueller, Wolfram; Gassler, Nikolaus; Schnabel, Philipp A.; Dienemann, Hendrik; Marme, Alexander; Hohenfellner, Markus; Haferkamp, Axel; Pfitzenmaier, Jesco; Groene, Hermann-Josef; Kolb, Armin; Buechler, Peter; Buechler, Markus W.; Friess, Helmut; Rittgen, Werner; Edler, Lutz; Debatin, Klaus-Michael; Krammer, Peter H.; Rutz, Hans P.; Herr, Ingrid. Research Group Molecular OncoSurgery, University of Heidelberg, Heidelberg, Germany. Cancer Biology & Therapy (2007), 6(2), 278-287. Publisher: Landes Bioscience, CODEN: CBTAAO ISSN: 1538-4047. Journal written in English. CAN 147:479951 AN 2007:1039338 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Glucocorticoids have been used widely in conjunction with cancer therapy due to their ability to induce apoptosis in hematol. cells and to prevent nausea and emesis. However, recent data including ours, suggest induction of therapy-resistance by glucocorticoids in solid tumors, although it is unclear whether this happens only in few carcinomas or is a more common cell type specific phenomenon. We performed an overall statistical anal. of our new and recent data obtained with 157 tumor probes evaluated in vitro, ex vivo and in vivo. The effect of glucocorticoids on apoptosis, viability and cell cycle progression under diverse clin. important questions was examd. New in vivo results demonstrate glucocorticoid-induced chemotherapy resistance in xenografted prostate cancer. In an overall statistical anal. we found glucocorticoid-induced resistance in 89% of 157 analyzed tumor samples. Resistance is common for several cytotoxic treatments and for several glucocorticoid-derivs. and due to an inhibition of apoptosis, promotion of viability and cell cycle progression. Resistance occurred at clin. achievable peak plasma levels of patients under anti-emetic glucocorticoid therapy

and below, lasted for a long time, after one single dose, but was reversible upon removal of glucocorticoids. Two nonsteroidal alternative anti-emetic agents did not counteract anticancer treatment and may be sufficient to replace glucocorticoids in cotreatment of carcinoma patients. These data demonstrate the need for prospective clin. studies as well as for detailed mechanistic studies of GC-induced cell-type specific pro- and anti-apoptotic signaling.

Answer 3:

Bibliographic Information

Methylseleninic acid enhances the effect of etoposide to inhibit prostate cancer growth in vivo. Gonzalez-Moreno, Oscar; Segura, Victor; Serrano, Diego; Nguewa, Paul; de las Rivas, Javier; Calvo, Alfonso. Division of Oncology, Center for Applied Medical Research (CIMA), University of Navarra, Pamplona, Spain. International Journal of Cancer (2007), 121(6), 1197-1204. Publisher: Wiley-Liss, Inc., CODEN: IJCNAW ISSN: 0020-7136. Journal written in English. CAN 147:291616 AN 2007:1005595 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

New therapeutic agents are needed for the treatment of androgen-independent prostate cancer (PrCa). We have investigated the effect of methylseleninic acid (MSA) on tumor stage-specific prostate cells derived from the C3 (1)/Tag model for PrCa: Pr111, a slow-growing and nontumorigenic cell line isolated from a prostate intraepithelial neoplasia lesion; Pr14, a tumorigenic line derived from a primary tumor; and Pr14C1, a sub-clone of Pr14 explanted from a lung metastasis. We demonstrate that MSA strongly inhibits cell growth and induces apoptosis in C3 (1)/Tag tumor cells, in a dose-dependent manner. A decrease in phosphorylated ERK1/2 and AKT was also found in tumor cells, but not in Pr111. Microarray anal. using affymetrix showed that the no. of genes with an altered expression in tumor cells is significantly higher ($p < 0.01$) than in nontumoral cells. Pathways analyses revealed a decrease in the expression of genes involved in metab. (Fabp5, Cyba), signal transduction (ERK, AKT), angiogenesis (neuropilin-1, Flt-4) and transcription (cAMP response element-binding protein) in tumor cells. The expression of neuropilin-1, a protein involved in VEGF signaling and tumor angiogenesis, was 97-fold repressed in Pr14 cells treated with MSA. Combination treatments using low doses of etoposide or taxotere (docetaxel), plus low doses of MSA revealed a strong enhancement of cell growth inhibition and apoptosis in tumor cells. Our in vivo studies using Pr14 cells xenografted into nude mice demonstrated that MSA significantly enhances the chemotherapeutical effect of etoposide, resulting in 78.3% tumor growth inhibition. These results suggest that MSA could be used against PrCa to enhance the effect of etoposide.

Answer 4:

Bibliographic Information

Predicting the active doses in humans from animal studies: a novel approach in oncology. Rocchetti, M.; Simeoni, M.; Pesenti, E.; De Nicolao, G.; Poggesi, I. Preclinical Development, Nerviano Medical Sciences, Nerviano, Italy. European Journal of Cancer (2007), 43(12), 1862-1868. Publisher: Elsevier Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 147:461695 AN 2007:895461 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The success rate of clin. drug development is significantly lower in oncol. than in other therapeutic areas. Predicting the activity of new compds. in humans from preclin. data could substantially reduce the no. of failures. A novel approach for predicting the expected active doses in humans from the first animal studies is presented here. The method relies upon a PK/PD model of tumor growth inhibition in xenografts, which provides parameters describing the potency of the tested compds. Anticancer drugs, currently used in the clinic, were evaluated in xenograft models and their potency parameters were estd. A good correlation was obtained between these parameters and the exposures sustained at the therapeutically relevant dosing regimens. Based on the corresponding regression equation and the potency parameters estd. in the first preclin. studies, the therapeutically active concns. of new compds. can be estd. An early knowledge of level of exposure or doses to be reached in humans will improve the risk evaluation and decision making processes in anticancer drug development.

Answer 5:

Bibliographic Information

G3139 and Other CpG-Containing Immunostimulatory Phosphorothioate Oligodeoxynucleotides Are Potent Suppressors of the Growth of Human Tumor Xenografts in Nude Mice. Gekeler, Volker; Gimmnich, Petra; Hofmann, Hans-Peter; Grebe, Carola; Roemmele, Michaela; Leja, Astrid; Baudler, Monika; Benimetskaya, Luba; Gonser, Barbara; Pieles, Uwe; Maier, Thomas; Wagner, Thomas; Sanders, Karl; Beck, James F.; Hanauer, Guido; Stein, C. A. ALTANA Pharma AG, Konstanz, Germany. Oligonucleotides (2006), 16(1), 83-93. Publisher: Mary Ann Liebert, Inc., CODEN: OLIGAJ ISSN: 1545-4576. Journal written in English. CAN 145:116878 AN 2006:307685 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Several phosphorothioate antisense oligodeoxynucleotides (ODN) are developed to target factors potentially involved in tumor growth and apoptosis suppression. Among them, the 18-mer G3139 (Oblimersen), which targets Bcl-2, is currently being tested in phase II and phase III clin. trials for various tumors in combination with chemotherapy. On the other hand, ODNs contg. CpG dinucleotides (CpG-ODN) within specific-sequence contexts (CpG motifs) have been shown to activate rodent or primate immune cells via toll-like receptor 9 (TLR9) and have demonstrated remarkable T cell-dependent antitumor efficacy in a series of murine tumor models. However, immune cell activation by CpG-ODN is largely diminished upon C-5 methylation at CpG cytosine. As G3139 contains CpG motifs, the authors questioned whether the antitumor effects seen in human tumor xenografts might be abrogated by cytosine C-5 methylation of G3139, which retained the ability of G3139 to suppress Bcl-2 expression in tissue culture, or by similar derivatization of other phosphorothioate ODNs developed for the immune activation of rodent or human cells. The in vivo antitumor efficacy of the immunostimulatory H1826 and H2006 ODNs was compared with that of G3139. Bcl-2 suppression achieved by G3139 purportedly sensitizes tumor cells toward cytotoxic agents, and some of the expts. employed combinations of ODN with such drugs as cisplatin or etoposide. H1826, H2006, and G3139 all produced similar, striking, growth inhibitory effects on either H69 SCLC, A2780 ovarian carcinoma, or A549 lung adenocarcinoma human tumor xenografts at doses of 0.3 mg/kg and 1 mg/kg (H1826, H2006) or 12 mg/kg (G3139) per day. In contrast, the H2006-mC (1 mg/kg) or G3139-mC (12 mg/kg) derivs. demonstrated no significant antitumor effects. The combination of G3139 (12 mg/kg) with cisplatin produced some additive antitumor efficacy, which was not seen in combinations of G3139-mC (12 mg/kg) or H1826 (1 mg/kg) with cisplatin.

G3139, at a dose of 12 mg/kg, alone induced extensive enlargement of the spleen. Immunostimulation was evaluated in vitro by flow cytometric measurements of the CD80 and CD86 activation markers found on CD19+ murine splenocytes. The CpG-ODN producing strong antitumor effects in vivo also induced these activation markers in vitro, in contrast to the in vivo inactive G3139-mC. Our data indicate a significant contribution of the immunostimulatory properties of CpG-ODN (including G3139) to the antitumor effects obsd. in nude mouse xenograft models. This is in contrast to previous data presented by other authors indicating that the activity of G3139 in human tumor xenografts was Bcl-2 specific. Furthermore, as nude mice are devoid of T cells, a T cell-mediated immune response apparently is not required for the potent antitumor responses obsd. here; innate immune responses are sufficient.

Answer 6:

Bibliographic Information

No topoisomerase I alteration in a neuroblastoma model with in vivo acquired resistance to irinotecan. Calvet, L.; Santos, A.; Valent, A.; Terrier-Lacombe, M-J.; Opolon, P.; Merlin, J-L.; Aubert, G.; Morizet, J.; Schellens, J. H. M.; Benard, J.; Vassal, G. Pharmacology and New Treatments in Cancer (UPRES EA 3535), Institut Gustave-Roussy, Villejuif, Fr. British Journal of Cancer (2004), 91(6), 1205-1212. Publisher: Nature Publishing Group, CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 142:169216 AN 2004:824732 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

CPT-11 (irinotecan) is a DNA-topoisomerase I inhibitor with preclin. activity against neuroblastoma (NB) xenografts. The aim was to establish in vivo an NB xenograft resistant to CPT-11 in order to study the resistance mechanisms acquired in a therapeutic setting.

IGR-NB8 is an immature NB xenograft with MYCN amplification and 1p deletion, which is sensitive to CPT-11. Athymic mice bearing advanced-stage s.c. tumors were treated with CPT-11 (27 mg kg-1 day-1 × 5) every 21 days (1 cycle) for a max. of four cycles. After tumor regrowth, a new in vivo passage was performed and the CPT-11 treatment was repeated. After the third passage, a resistant xenograft was obtained (IGRNB8-R). The tumor growth delay (TGD) was reduced from 115 at passage 1 to 40 at passage 4 and no complete or partial regression was obsd. After further exposure to the drug, up to 28 passages, the resistant xenograft was definitively established with a TGD from 17 at passage 28. Resistant tumors reverted to sensitive tumors after 15 passages without treatment. IGR-NB8-R remained sensitive to cyclophosphamide and cisplatin and cross-resistance was obsd. with the topoisomerase I inhibitor topotecan. No quant. or qual. topoisomerase I modifications were obsd. The level of expression of multidrug resistance 1 (MDR1), MDR-assocd. protein 1 (MRP1) and, breast cancer resistance protein, three members of the ATP-binding cassette transporter family was not modified over passages. Our results suggest a novel resistance mechanism, probably not involving the mechanisms usually obsd. in vitro.

Answer 7:

Bibliographic Information

In vitro and in vivo evaluation of the influence of type III NaPi co-transporter activity during apoptosis on 99mTc-(V)DMSA uptake in the human leukaemic cell line U937. Denoyer, Delphine; Perek, Nathalie; Le Jeune, Nathalie; Frere, Delphine; Sabido, Odile; Clotagatide, Anthony; Dubois, Francis. Department of Biophysics and Radiopharmaceuticals, "Cell Survival and Adhesion" Research Group, University of Saint-Etienne, Saint-Etienne, Fr. European Journal of Nuclear Medicine and Molecular Imaging (2004), 31(10), 1421-1427. Publisher: Springer GmbH, CODEN: EJNMA6 ISSN: 1619-7070. Journal written in English. CAN 141:363668 AN 2004:769418 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Pentavalent 99mTc-dimercaptosuccinic acid [99mTc-(V)DMSA or (V)DMSA] is a marker of phosphate transport, entering cells specifically through type III NaPi co-transporters. Phosphate ion is known to be involved in cell metab., including the apoptotic cell death process. As phosphate accumulation decreases during apoptosis, we investigated the influence of type III NaPi co-transporter activity on (V)DMSA uptake during this type of cell death. Uptake of (V)DMSA and phosphate was compared in a leukemic cell line (U937) in vitro model after induction of apoptosis by a chemotherapeutic agent, etoposide (VP16). (V)DMSA biodistribution in nude mice during apoptosis was also investigated in a U937 xenograft in vivo model. The percentage of apoptosis in vitro and ex vivo was detd. with annexin V fluorescein by flow cytometry. The in vitro results showed that, in parallel with the decrease in phosphate uptake during apoptosis, (V)DMSA accumulation is neg. correlated with the percentage of apoptosis. Biodistribution studies showed decreased accumulation of (V)DMSA in tumors after treatment with VP16. Animal studies also confirmed an inverse correlation between percentage of apoptosis in tumors and (V)DMSA uptake. The activity of type III NaPi co-transporter is inhibited during the early stages of apoptosis, leading to differential incorporation of (V)DMSA in viable cells and apoptotic cells both in vitro and in vivo.

Answer 8:

Bibliographic Information

Clonogenic assay with established human tumour xenografts: correlation of in vitro to in vivo activity as a basis for anticancer drug discovery. Fiebig, H. H.; Maier, A.; Burger, A. M. Oncotest GmbH, Institute for Experimental Oncology, Freiburg, Germany. European Journal of Cancer (2004), 40(6), 802-820. Publisher: Elsevier Science Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 141:342988 AN 2004:284718 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Pluripotent cells can be grown in clonogenic assays. The tumor stem-cell fraction, which accounts for <0.4% of the total cells, and which is considered the most relevant cell type in the development of metastases and recurrences, is able to divide and to form colonies in a semisolid matrix (agar or methylcellulose). Major applications of the tumor clonogenic assay (TCA) are chemosensitivity

testing of tumors and xenografts, and for assessments within drug discovery programs. Of crit. relevance for the usefulness of the TCA is whether it can predict sensitivity or resistance towards clin. used agents. When we compared the response of human tumors established as xenografts in nude mice in the TCA in vitro to that of the clin. response, 62% of the comparisons for drug sensitivity, and 92% of the comparisons for drug resistance were correct. The same percentage of true/false observations was found when tumors were tested after serial passage in nude mice in the TCA in vitro and their response compared to in vivo activity in corresponding xenografts (60% and 90%, resp.). The highest correct predictive values were, however, found when the clin. response of tumors was compared to their explants established in the nude mouse and treated in vivo. Of 80 comparisons performed, we obsd. a correct prediction for tumor resistance in 97% and for tumor sensitivity in 90%. In our opinion, the TCA with established human tumor xenografts has an important role in current drug discovery strategies. We therefore included the TCA as secondary assay in our approach to anticancer drug discovery and found that a no. of novel agents were active; these are now in advanced preclin. development or clin. trials. Thus, the tumor clonogenic assay has proven predictive value in the chemosensitivity testing of std. and exptl. anticancer drugs.

Answer 9:

Bibliographic Information

In vivo antitumor activity of a novel sulfonamide, HMN-214, against human tumor xenografts in mice and the spectrum of cytotoxicity of its active metabolite, HMN-176. Takagi, Manabu; Honmura, Takuya; Watanabe, Shuuji; Yamaguchi, Reiko; Nogawa, Masaki; Nishimura, Ikumi; Katoh, Fumitaka; Matsuda, Masato; Hidaka, Hiroyoshi. Discovery Research Laboratories and Developmental Research Laboratories, Nippon Shinyaku Co., Kyoto, Japan. Investigational New Drugs (2003), 21(4), 387-399. Publisher: Kluwer Academic Publishers, CODEN: INNDDK ISSN: 0167-6997. Journal written in English. CAN 141:16960 AN 2003:833144 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The cytotoxic effects of HMN-176 ((E)-4-{[2-N-[4-methoxybenzenesulfonyl] amino] stilbazole} 1-oxide; Figure 1), a newly synthesized compd., were evaluated and compared with those of the clin. used antitumor agents cis-platinum, adriamycin, etoposide, taxol, and vincristine in 22 human tumor cell lines isolated from various organs. HMN-176 exhibited potent cytotoxicity with IC50 values in the nM range, and the variance of its cytotoxic efficacy was remarkably small. Drug-resistant cell lines also showed low cross-resistance to HMN-176 corresponding to overall resistance indexes of less than 14.3. HMN-214 was synthesized as an oral prodrug because of the poor oral absorption of HMN-176 itself. Pharmacokinetic studies showed that HMN-214 was an acceptable oral prodrug of HMN-176. In the in vivo anal. of the schedule-dependency of HMN-214, the repeated administration for over 5 days elicited potent antitumor activity, as expected from the exposure-dependency of the cytotoxicity of HMN-176 and from the cytometric studies. The antitumor activity of HMN-214 against human tumor xenografts was equal or superior to that of clin. available agents, including cis-platinum, adriamycin, vincristine, and UFT without severe toxicity such as neurotoxicity. Because of its good activity in preclin. trials, HMN-214 has entered Phase I clin. trials in the USA.

Answer 10:

Bibliographic Information

Pk 11195, a mitochondrial benzodiazepine receptor antagonist, reduces apoptosis threshold in Bcl-XL and Mcl-1 expressing human cholangiocarcinoma cells. Okaro, A. C.; Fennell, D. A.; Corbo, M.; Davidson, B. R.; Cotter, F. E. Department of Experimental Haematology, St. Bartholomew's and the Royal London School of Medicine, London, UK. Gut (2002), 51(4), 556-561. Publisher: BMJ Publishing Group, CODEN: GUTTAK ISSN: 0017-5749. Journal written in English. CAN 139:270425 AN 2003:171552 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Cholangiocarcinoma cells express high levels of the antiapoptotic proteins Bcl-XL and Mcl-1 and are markedly chemo-andradioresistant. Mitochondria have emerged as central players in apoptosis. Antiapoptotic members of the Bcl-2 protein family

localise to the outer mitochondrial membrane and regulate mitochondrial release of apoptogenic proteins. Mitochondrial benzodiazepine receptor (mBzR) ligands have been shown to reverse Bcl-2 action and facilitate apoptosis. We evaluated the ability of the mBzR antagonist Pk11195 to overcome preapoptotic mitochondrial dysfunction in Egi-1 and Tfk-1, two human cholangiocarcinoma cell lines expressing high levels of Bcl-XL and Mcl-1. Cells growing in culture were used to perform in vitro expts. over 48 -9 6 h following treatment. The cytotoxic agents used were 5 fluorouracil 10 μM and etoposide (Vp16) 10 μM, together with UV and 0.5 - 1 Gy x ray irradn. with or without 75 μM Pk11195. Apoptosis and mitochondrial dysfunction were measured at single cell resoln. by flow cytometry using the mitochondrial fluorochrome DiOC6(3). Severe combined immunodeficient non-obese diabetic (SCID-NOD) mice with s.c. xenografts using the Egi-1 and Tfk-1 cell lines were treated with etoposide with or without addn. of Pk11195 over a 72 h period during which time the xenograft growth patterns were monitored. In vitro, the effect of Pk11195 on induction of apoptosis in cholangiocarcinoma cells following stimulation by chemotherapy or radiotherapy was found to be both time and dose dependent, with Pk11195 increasing rates of apoptosis by 50 - 95%. I.p. administration of Pk11195 in combination with Vp16 was found to increase the growth inhibiting effects of Vp16 on xenografts during the treatment phase. PK11195 75 μM on its own had no intrinsic cytotoxic efficacy. This is the first study to demonstrate that functional antagonism of coexpressed Bcl-XL and Mcl-1 proteins using the mBzR antagonist Pk11195 can facilitate apoptosis in cholangiocarcinoma following chemotherapy and radiotherapy.

Answer 11:

Bibliographic Information

Effect of a novel somatostatin analogue combined with cytotoxic drugs on human tumor xenografts and metastasis of B16 melanoma. Szende, B.; Horvath, A.; Boekoenyi, G.; Keri, G. 1st Dept. of Pathology and Experimental Cancer Res., Semmelweis Univ., Budapest, Hung. British Journal of Cancer (2003), 88(1), 132-136. Publisher: Nature Publishing Group, CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 139:271238 AN 2003:71031 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A novel somatostatin analog, TT-232 (which inhibits the proliferation of various cell cultures and transplantable mouse tumors), was examd. regarding its effect on human melanoma and lymphoma xenografts as a single treatment or in combination with DTIC (dacarbazine) and etoposide. TT-232 inhibited the growth of HT-18 melanoma xenografts, a dose of 5 mg kg-1 being the most effective. Combination of 1 mg kg-1 TT-232 with 30 or 60 mg kg-1 DTIC (administered daily) resulted in a stronger inhibitory effect compared to TT-232 or DTIC as a single modality. Antimetastatic effect of TT-232 treatment combined with DTIC was studied using the B16 mouse melanoma muscle-lung metastasis model. The no. of lung metastases of B16 melanoma could be decreased by the daily administration of 1 mg kg-1 TT-232 or 60 mg kg-1, but not of 30 mg kg-1 DTIC. TT-232, combined with 30 or 60 mg kg-1 DTIC decreased the lung metastasis no. significantly lower than the control. Nearly 50% growth inhibition of HT-58 lymphoma was achieved by daily treatment with 1 mg kg-1 TT-232. 5 mg kg-1 etoposide, administered daily, resulted in a similar effect. The combination of 1 mg kg-1 TT-232 and 5 mg kg-1 etoposide was significantly more effective than TT-232 or etoposide as a single treatment. The very strong tumor growth inhibitory effect of 10 mg kg-1 etoposide could even be increased by combination with TT-232. These exptl. data suggest that TT-232 may be an effective new tool in the combination chemotherapy of malignant tumors like melanoma and lymphoma.

Answer 12:

Bibliographic Information

Peripheral benzodiazepine receptor ligands reverse apoptosis resistance of cancer cells in vitro and in vivo. Decaudin, Didier; Castedo, Maria; Nemati, Fariba; Beurdeley-Thomas, Arnaud; De Pinieux, Gonzague; Caron, Antoine; Pouillart, Pierre; Wijdenes, John; Rouillard, Dany; Kroemer, Guido; Poupon, Marie-France. Departments of Hematology and UMR 147 CNRS, Section de Recherche, Institut Curie, Paris, Fr. Cancer Research (2002), 62(5), 1388-1393. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 137:134621 AN 2002:226277 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The mitochondrial peripheral benzodiazepine receptor (mPBR) is involved in a functional structure designated as the permeability transition pore, which controls apoptosis. Binding of Fas/APO-1/CD95 triggers a prototypic apoptosis-inducing pathway. Using four different human tumor cell lines (T-cell Jurkat, neuroblastoma SHEP, osteosarcoma 143N2, and glioblastoma SNB79 cell lines), all of which express CD95 and mPBR, the authors investigated the potential role of mPBR ligands in CD95-induced apoptosis. The authors show that, in vitro, the three mPBR ligands tested (RO5-4864, PK11195, and diazepam) enhanced apoptosis induced by anti-CD95 antibody in Jurkat cells, as demonstrated by mitochondrial transmembrane potential drop and DNA fragmentation. In contrast, RO5-4864, but not PK11195 or diazepam, enhanced anti-CD95 apoptosis in all other cell lines. These effects were obtained in Bcl-2-overexpressing SHEP cell lines, but not in Bcl-XL SHEP cell lines. Enhancement of anti-CD95 antibody-induced apoptosis by RO5-4864 was characterized by an increased mitochondrial release of cytochrome c and Smac/DIABLO proteins and an enhanced activation of caspases 9 and 3, suggesting a mitochondrion-dependent mechanism. Preincubation of cells with the different mPBR ligands or anti-CD95 did not affect the levels of expression of either mPBR or CD95. In vivo, the authors found that the RO5-4864 mPBR ligand significantly increased the growth inhibition induced by two chemotherapeutic agents, etoposide and ifosfamide, using two human small cell lung cancers xenografted into nude mice. Peripheral benzodiazepine receptor ligands may therefore act as chemosensitizing agents for the treatment of human neoplasms.

Answer 13:

Bibliographic Information

Efficient carboplatin single therapy in a mouse model of human testicular nonseminomatous germ cell tumor. Aharinejad, Seyedhossein; Fink, Melanie; Abri, Hojatollah; Nedwed, Stephan; Schlag, Michael G.; MacFelda, Karin; Abraham, Dietmar; Miksovsky, Aurelia; Holtl, Eva; Holtl, Wolfgang. Laboratory for Cardiovascular Research, Department of Anatomy, Center for Biomedical Research, University of Vienna, Vienna, Austria. Journal of Urology (Hagerstown, MD, United States) (2002), 167(1), 368-374. Publisher: Lippincott Williams & Wilkins, CODEN: JOURAA ISSN: 0022-5347. Journal written in English. CAN 137:119162 AN 2002:37948 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

To decrease morbidity of cisplatin-based combination therapy, carboplatin vs. etoposide single therapy was examd. in an animal model. SCID mice bearing testicular nonseminomatous germ cell tumor xenografts received 120 mg carboplatin/kg as a single cycle, 60 or 30 mg carboplatin/kg cycled twice, 80, 50 or 30 mg etoposide/kg cycled twice, or Ringer's soln. Histol. and immunocytochem. testing, in vivo microscopy, vascular corrosion casting, serum tumor markers, complete blood count and real-time polymerase chain reaction were used to monitor therapy efficacy. Carboplatin at 60 mg/kg cycled twice eradicated the tumor and reduced vascular d. and vascular endothelial growth factor-A mRNA. Elevated tumor markers returned to basal values after carboplatin administration. Therapy was well tolerated; thrombocytopenia had disappeared 6 wk after therapy and the animals were tumor-free 6 mo after treatment. Although 120 mg carboplatin/kg eradicated the tumor, it resulted in extensive mortality and morbidity. Single treatment with 30, 50 and 80 mg etoposide/kg failed. Carboplatin single therapy was highly effective in this nonseminomatous germ cell tumor model and it may be useful in future clin. trials in patients with high-risk stage I nonseminomatous germ cell cancer for reducing morbidity from cisplatin-based combination therapy. Vascular d. and vascular endothelial growth factor mRNA were elevated in this animal model and deserve further study as potential risk factors in nonseminomatous germ cell tumor cases.

Answer 14:

Bibliographic Information

The synthesis, discovery, and development of a highly promising class of microtubule stabilization agents: curative effects of desoxyepothilones B and F against human tumor xenografts in nude mice. Chou, Ting-Chao; O'Connor, Owen A.; Tong, William P.; Guan, Yongbiao; Zhang, Zui-Guo; Stachel, Shawn J.; Lee, Chulbom; Danishefsky, Samuel J. Preclinical Pharmacology Core Facility, Memorial Sloan-Kettering Cancer Center, New York, NY, USA. Proceedings of the National Academy of Sciences of the United States of America (2001), 98(14), 8113-8118. Publisher: National Academy of Sciences, CODEN: PNASA6 ISSN: 0027-8424. Journal written in English. CAN 135:327022 AN 2001:526491 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We have evaluated two synthetic epothilone analogs lacking the 12,13-epoxide functionality, 12,13-desoxyepothilone B (dEpoB), and 12,13-desoxyepothilone F (dEpoF). The concns. required for 50% growth inhibition (IC50) for a variety of anticancer agents were measured in CCRF-CEM/VBL1000 cells (2,048-fold resistance to vinblastine). By using dEpoB, dEpoF, aza-EpoB, and paclitaxel, the IC50 values were 0.029, 0.092, 2.99, and 5.17 μM, resp. These values represent 4-, 33.5-, 1,423- and 3,133-fold resistance, resp., when compared with the corresponding IC50 in the parent [nonmultiple drug-resistant (MDR)] CCRF-CEM cells. We then produced MDR human lung carcinoma A549 cells by continuous exposure of the tumor cells to sublethal concns. of dEpoB (1.8 yr), vinblastine (1.2 yr), and paclitaxel (1.8 yr). This continued exposure led to the development of 2.1-, 4,848-, and 2,553-fold resistance to each drug, resp. The therapeutic effect of dEpoB and paclitaxel was also compared in vivo in a mouse model by using various tumor xenografts. DEpoB is much more effective in reducing tumor sizes in all MDR tumors tested. Anal. of dEpoF, an analog possessing greater aq. soly. than dEpoB, showed curative effects similar to dEpoB against K562, CCRF-CEM, and MX-1 xenografts. These results indicate that dEpoB and dEpoF are efficacious antitumor agents with both a broad chemotherapeutic spectrum and wide safety margins.

Answer 15:

Bibliographic Information

Anti-interleukin-6 monoclonal antibody induces regression of human prostate cancer xenografts in nude mice. Smith, Peter C.; Keller, Evan T. Unit for Laboratory Animal Medicine, University of Michigan, Ann Arbor, MI, USA. Prostate (New York, NY, United States) (2001), 48(1), 47-53. Publisher: Wiley-Liss, Inc., CODEN: PRSTDS ISSN: 0270-4137. Journal written in English. CAN 136:165745 AN 2001:507302 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Despite clin. assocns. and in vitro data suggesting that autocrine interleukin-6 (IL-6) prodn. contributes to prostate cancer progression or chemotherapy resistance, there have been no reports that explore the role of IL-6 on prostate tumors in vivo. In the present study, the authors investigated the effect of IL-6 inhibition on the growth of human prostate cancer xenografts in nude mice. To det. if autocrine IL-6 prodn. contributes to prostate cancer growth and chemotherapy resistance in vivo, xenografts of a human prostate cancer cell line that produces IL-6 (PC-3) were established in nude mice. The mice were randomly divided into four treatment groups: (1) saline (vehicle control) + murine IgG (isotype control); (2) etoposide + murine IgG; (3) saline + anti-IL-6 monoclonal antibody; and (4) etoposide + anti-IL-6 monoclonal antibody. Tumors were measured twice weekly during a 4-wk treatment period. At the conclusion of the study, all mice were sacrificed, and in addn. to final vol., tumors were evaluated for the degree of apoptosis by TUNEL anal. Anti-IL-6 Ab (with saline or etoposide) induced tumor apoptosis and regression (.apprx.60% compared to initial tumor size). Etoposide alone did not induce tumor regression or apoptosis in this animal model, and there was no synergy between anti-IL-6 Ab and etoposide. These studies suggest that IL-6 contributes to prostate cancer growth in vivo, and that targeting IL-6 may contribute to prostate cancer therapy.

Answer 16:

Bibliographic Information

In vivo antitumor efficacy of MGI-114 (6-hydroxymethylacylfulvene, HMAF) in various human tumor xenograft models including several lung and gastric tumors. Sato, Y.; Kashimoto, S.; MacDonald, J. R.; Nakano, K. Discovery Research Laboratories, Department of Pharmacology II, Dainippon Pharmaceutical Co., Ltd., Suita, Osaka, Japan. European Journal of Cancer (2001), 37(11), 1419-1428. Publisher: Elsevier Science Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 136:288614 AN 2001:483139 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The in vivo antitumor efficacy of MGI-114 (a semisynthetic analog of the cytotoxic sesquiterpenoid illudins) was examd. in a panel of human tumor xenografts in mice, consisting mainly of human lung and gastric tumors, and compared with that of other antitumor drugs (irinotecan, paclitaxel, cisplatin, doxorubicin, vindesine, etoposide and 5-fluorouracil). When different administration schedules were

compared, daily administration of MGI-114 was more effective than intermittent administrations. In human tumor xenograft models of nasopharyngeal, breast and colon carcinoma and melanoma, MGI-114 exerted a strong antitumor activity, with complete tumor regression occurring. Moreover, in four human lung and three gastric tumor xenografts, MGI-114 had a strong antitumor activity, with complete tumor regression occurring in some cases. The antitumor efficacy of MGI-114 was generally higher than or equiv. to that of irinotecan and paclitaxel. These results support the potential utility of MGI-114 in the treatment of a variety of human solid tumors.

Answer 17:

Bibliographic Information

In vitro and in vivo reversal of P-glycoprotein-mediated multidrug resistance by a novel potent modulator, XR9576. Mistry, Prakash; Stewart, Alistair J.; Dangerfield, Wendy; Okiji, Sade; Liddle, Chris; Bootle, Douglas; Plumb, Jane A.; Templeton, David; Charlton, Peter. Xenova Limited, Slough, UK. Cancer Research (2001), 61(2), 749-758. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 134:305064 AN 2001:125551 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The overexpression of P-glycoprotein (P-gp) on the surface of tumor cells causes multidrug resistance (MDR). This protein acts as an energy-dependent drug efflux pump reducing the intracellular concn. of structurally unrelated drugs. Modulators of P-gp function can restore the sensitivity of MDR cells to such drugs. XR9576 is a novel anthranilic acid deriv. developed as a potent and specific inhibitor of P-gp, and in this study we evaluate the in vitro and in vivo modulatory activity of this compd. The in vitro activity of XR9576 was evaluated using a panel of human (H69/LX4, 2780AD) and murine (EMT6 AR1.0, MC26) MDR cell lines. XR9576 potentiated the cytotoxicity of several drugs including doxorubicin, paclitaxel, etoposide, and vincristine; complete reversal of resistance was achieved in the presence of 25-80 nM XR9576. Direct comparative studies with other modulators indicated that XR9576 was one of the most potent modulators described to date. Accumulation and efflux studies with the P-gp substrates, [3H]daunorubicin and rhodamine 123, demonstrated that XR9576 inhibited P-gp-mediated drug efflux. The inhibition of P-gp function was reversible, but the effects persisted for > 22 h after removal of the modulator from the incubation medium. This is in contrast to P-gp substrates such as cyclosporin A and verapamil, which lose their activity within 60 min, suggesting that XR9576 is not transported by P-gp. Also, XR9576 was a potent inhibitor of photoaffinity labeling of P-gp by [3H]azidopine implying a direct interaction with the protein. In mice bearing the intrinsically resistant MC26 colon tumors, coadministration of XR9576 potentiated the antitumor activity of doxorubicin without a significant increase in toxicity; max. potentiation was obsd. at 2.5-4.0 mg/kg dosed either i.v. or p.o.

In addn., coadministration of XR9576 (6-12 mg/kg p.o.) fully restored the antitumor activity of paclitaxel, etoposide, and vincristine against two highly resistant MDR human tumor xenografts (2780AD, H69/LX4) in nude mice. Importantly all of the efficacious combination schedules appeared to be well tolerated. Furthermore, i.v. coadministration of XR9576 did not alter the plasma pharmacokinetics of paclitaxel. These results demonstrate that XR9576 is an extremely potent, selective, and effective modulator with a long duration of action. It exhibits potent i.v. and p.o. activity without apparently enhancing the plasma pharmacokinetics of paclitaxel or the toxicity of coadministered drugs. Hence, XR9576 holds great promise for the treatment of P-gp-mediated MDR cancers.

Answer 18:

Bibliographic Information

Distinctive potentiating effects of cisplatin and/or ifosfamide combined with etoposide in human small-cell lung carcinoma xenografts. Nemati, Fariba; Livartowski, Alain; De Cremoux, Patricia; Bourgeois, Yveline; Arvelo, Francisco; Pouillart, Pierre; Poupon, Marie-France. Centre National de la Recherche Scientifique, Institut Curie, Paris, Fr. Clinical Cancer Research (2000), 6(5), 2075-2086. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 133:275871 AN 2000:401148 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Xenografts (in mice) of small-cell lung carcinoma (SCLC) from eight patients were used to test the tumor sensitivity to etoposide (VP16; 12-16 mg/kg/day, days 1, 2, and 3), cisplatin (CDDP; 6-9 mg/kg/day, day 1) and ifosfamide (IFO; 90-210 mg/kg/day, days 1, 2, and 3) as single agents and to evaluate the efficacy of 2-drug or 3-drug combinations. Five xenografts came from untreated patients (SCLC-61, SCLC-6, SCLC-10, SCLC-41, and SCLC-96) and three after treatment (SCLC-74, SCLC-101, and SCLC-108). P53 was inactivated in all of them. Tumor growth inhibition, growth delay, and the survival rate of tumor-bearing mice reflected individual SCLC chemosensitivity. As single agents, IFO inhibited tumor growth in a dose-dependent manner, whereas CDDP and VP16 had little or no effect. Both CDDP and IFO potentiated VP16, inducing complete regressions in the most sensitive SCLCs; VP16-IFO was more effective than VP16-CDDP, with complete regressions in six vs. three of the eight tumors tested, resp. CDDP-IFO was less effective than VP16-IFO, with three of eight SCLCs giving complete regressions. The 3-drug combination led to modest improvement over the best 2-drug combination but only for sensitive SCLCs. Because the drug responses distinguished two classes of SCLCs, as sensitive or refractory, MDR1, glutathione S-transferase π, lung-related multidrug resistance protein, multidrug resistance protein, and topoisomerase IIα mRNA expression was studied by semiquant. reverse transcription. There was no correlation with SCLC sensitivity; topoisomerase IIα and multidrug resistance protein were expressed in all cases, lung-related multidrug resistance protein and glutathione S-transferase π in seven of eight, and MDR1 gene in four of eight. In conclusion, these SCLC xenografts displayed a pattern of chemotherapy response close to that obsd. in patients.

This model confirmed that in 2-drug combinations, each component potentiated the effects of the other, with VP16-IFO tending to be the best 2-drug combination, both of which were more effective than VP16-CDDP and better tolerated than CDDP-IFO. The addn. of a 3rd agent gave only a modest, if any, therapeutic benefit in the responders but none in refractory SCLCs. There was no correlation between the extent of response and the expression of the resistance markers.

Answer 19:

Bibliographic Information

Evaluation of the antitumor activity of liposomal formulations of etoposide against choriocarcinoma xenografts in Balb/c nu/nu mice. Tyagi, P.; Sengupta, S.; Velpandian, T.; Gupta, Y. K.; Kochupillai, V.; Gupta, S. K. Department of Pharmacology, University of Cambridge, Cambridge, UK. Pharmacy and Pharmacology Communications (1999), 5(10), 595-598. Publisher: Royal Pharmaceutical Society of Great Britain, CODEN: PPCOFN ISSN: 1460-8081. Journal written in English. CAN 132:54735 AN 1999:763350 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Conventional delivery of etoposide for anticancer therapy is restricted by its lipophilicity and vehicle-assocd. adverse effects. Liposomes have been reported to increase the efficacy and reduce the toxicity of antineoplastic agents. This study was conducted to evaluate novel cationic and sterically-stabilized long-circulating pegylated liposomal formulations of etoposide against JEG3 cell-induced choriocarcinoma xenografts in Balb/c nu/nu mice. Small unilamellar liposomes loaded with etoposide were prepd. by thin-film hydration followed by an extrusion method. The total encapsulation of etoposide was 3.6 and 2.74 mol% for cationic and pegylated liposomes, resp. At a dose of 10 mg m-2/day for 5 days, both the formulations significantly delayed tumor growth and increased the lifespan of the host compared with conventional delivery of etoposide. Liposomes could thus be considered as potential useful carriers for the delivery of etoposide.

Answer 20:

Bibliographic Information

Evaluation of antitumor activity of etoposide administered orally for 21 consecutive days against human uterine cancer subcutaneous and/or orthotopic xenografts in nude mice. Matsumoto, Sayuri; Mashiba, Hiroko; Okamoto, Kazuya; Ekimoto, Hisao. Anticancer Drugs Dept., Research & Development Division, Pharmaceutical Group, Nippon Kayaku Co., Ltd, Japan. Gan to Kagaku Ryoho (1999), 26(9), 1313-1320. Publisher: Gan to Kagaku Ryohosha, CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 132:117203 AN 1999:634564 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The antitumor activity of etoposide (ETP) against human uterine cancer cell lines were investigated in vitro and in vivo. The cytotoxic activity of ETP against HeLa S3, a human cervical cancer cell line, depended on exposure time. The survival rate with 24 h prolonged exposure was reduced to about 1/200 that with 6 h exposure. The time dependency of antitumor activity of ETP against HeLa S3 s.c. transplanted in nude mice was studied. The effect of 21 or 28 consecutive days oral administration was greater than that of 5 or 14 consecutive days. Furthermore, a longer administration schedule was less toxic. The antitumor activity of ETP administered orally for 21 consecutive days was compared with that of CDDP, CPT-11 and 5'-DFUR using both human uterine cancer cell lines (TCO-1, SIHA, UCC08JCK) transplanted s.c. in nude mice and human uterine cancer cell lines (HeLa S3, UCC08JCK) transplanted into the uterus of nude mice. ETP showed the same antitumor activity as CPT-11 and 5'-DFUR against TCO-1 and UCC08JCK, human uterine cancer cell lines transplanted s.c. in nude mice. ETP also showed anticancer activity against two cell lines transplanted into the uterus. The growth inhibition caused by ETP administered orally at 50 mg/kg against HeLa S3 transplanted s.c. was 36.7% while that against the same cell line transplanted into the uterus was 58.5%. 5'-DFUR also showed the same antitumor activity as ETP. These results suggest that long term oral administration of ETP is clin. useful for cervical cancer patients.

Answer 21:

Bibliographic Information

Antitumor effect of CPT-11, a camptothecin derivative, on human testicular tumor xenografts in nude mice. Miki, Tsuneharu; Sawada, Masumi; Nonomura, Norio; Kojima, Yasuyuki; Okuyama, Akihiko; Maeda, Osamu; Saiki, Shigeru; Kotake, Toshihiko. Department of Urology, Osaka University Medical School, Osaka, Japan. European Urology (1997), 31(1), 92-96. Publisher: S. Karger AG, CODEN: EUURAV ISSN: 0302-2838. Journal written in English. CAN 129:285665 AN 1998:542001 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The antitumor effect of CPT-11, a camptothecin deriv., on two human testicular embryonal carcinomas (TTSC-2 and TTSC-3) heterotransplanted into nude mice was studied. Tumor-bearing nude mice were given daily i.p. injections of the anticancer drugs in 0.1 mL saline 3 times at 3-day intervals. At the end of the expts. tumors were resected and subjected to light-microscopic observation. When 10, 30 and 50 mg/kg of CPT-11 was administered to tumor-bearing mice i.p., the antitumor effect of CPT-11 was obsd. dose-dependently in both TTSC-2 and TTSC-3. When 30 mg/kg of CPT-11 was administered in combination with CDDP, complete tumor regression was obsd. in both TTSC-2 and TTSC-3 tumors. Histol. findings correlated well with the decrease in tumor vol. of treated tumors. No mice died after treatment with CPT-11 in a single-agent and combination chemotherapy. Chemotherapy with CPT-11 was an effective and safe method against human testicular tumors heterotransplanted in nude mice.

Answer 22:

Bibliographic Information

Multidrug resistance genes (MRP) and MDR1 expression in small cell lung cancer xenografts: relationship with response to chemotherapy. Canitrot, Yvan; Bichat, Francis; Cole, Susan P. C.; Deeley, Roger G.; Gerlach, James H.; Bastian, Gerard; Arvelo, Francisco; Poupon, Marie-France. Cancer Research Laboratories, Queen's University, Kingston, ON, Can. Cancer Letters (Shannon, Ireland) (1998), 130(1,2), 133-141. Publisher: Elsevier Science Ireland Ltd., CODEN: CALEDQ ISSN: 0304-3835. Journal written in English. CAN 129:310474 AN 1998:497582 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Intrinsic or acquired drug resistance is a major limiting factor of the effectiveness of chemotherapy. Increased expression of either the MRP gene or the MDR1 gene has been demonstrated to confer drug resistance in vitro. In this study, we examd. MRP and MDR1 gene expression in a panel of 17 small cell lung cancers (SCLC) xenografted into nude mice from treated and untreated patients using an RT-PCR technique. For some of them, the outcome of the corresponding patients was known and we related MDR1/MRP expression with the xenograft response to C'CAV (cyclophosphamide, cisplatin, adriamycin and etoposide) combined chemotherapy. Fifteen (88%) of the 17 cases of SCLC were found to be pos. for either MDR1 or MRP. MRP gene expression was present in 12 (71%)

of 17 cases, whereas MDR1 gene expression was detected in eight (50%) of 16 cases. For six SCLC, the survival duration of patients differed, with three patients surviving for >30 mo after therapy. Among these six tumors, five expressed MRP and/or MDR1. These six xenografts responded to the C'CAV treatment but a significant rate of cure was obtained in only three cases. No obvious relationship was obsd. between the response to this treatment and MRP or MDR1 expression. However, the remarkably high levels and frequency of MRP expression in some SCLC samples indicate that future developments in chemotherapy of this tumor type should anticipate that drugs which are substrates of MRP may be of limited effectiveness.

Answer 23:

Bibliographic Information

Use of the comet assay for assessment of drug resistance and its modulation in vivo. Huang, P.; Olive, P. L.; Durand, R. E. Medical Biophysics Department, BC Cancer Research Centre, Vancouver, BC, Can. British Journal of Cancer (1998), 77(3), 412-416. Publisher: Churchill Livingstone, CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 128:225605 AN 1998:109240 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Drug resistance is generally considered to be a major impediment to successful cancer chemotherapy, yet it is generally not possible to predict the degree or timing of the emergence of tumor resistance in most chemotherapy protocols. Recent developments with the single-cell gel electrophoresis or 'comet' assay for DNA damage at the single-cell level suggest that this technique might provide a method for identifying and potentially monitoring tumor cell responsiveness to many anti-cancer agents in situ. In principle, this assay could be applied to any accessible tumor being treated with chemotherapeutic agents that cause overt DNA damage. The authors have investigated that supposition using several rodent and human tumor cell lines exhibiting a spectrum of resistance to the DNA strand-breaking drug, etoposide. By assessing cells grown as monolayers, spheroids and xenografted tumors in immunodeficient mice, the authors found that the comet assay can provide not only an index of sensitivity to etoposide, but, addnl., can demonstrate the efficacy (or lack thereof) of multidrug resistance (MDR) reversing agents for cells in vitro, and tumors in vivo.

Answer 24:

Bibliographic Information

Potent therapeutic activity of irinotecan (CPT-11) and its schedule dependency in medulloblastoma xenografts in nude mice. Vassal, Gilles; Boland, Isabelle; Santos, Alexandre; Bissery, Marie-Christine; Terrier-Lacombe, Marie-Jose; Morizet, Jackie; Sainte-Rose, Christian; Lellouch-Tubiana, Arielle; Kalifa, Chantal; Gouyetre, Alain. Laboratory of Pharmacotoxicology and Pharmacogenetics (CNRS URA147), Institut Gustave-Roussy, Villejuif, Fr. International Journal of Cancer (1997), 73(1), 156-163. Publisher: Wiley-Liss, CODEN: IJCNAW ISSN: 0020-7136. Journal written in English. CAN 128:18460 AN 1997:693561 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The anti-tumor activity of irinotecan (CPT-11), a DNA-topoisomerase I inhibitor, was evaluated in 5 advanced stage s.c. medulloblastoma xenografts in nude mice, using different schedules of administration. With a 5-day schedule, the highest i.v. dose tested (40 mg kg-1 day-1) induced complete regressions in all xenografts but 1, and delays in tumor growth always exceeded 30 days. Two xenografts, IGRM11 and IGRM33, were highly sensitive, and animals survived tumor-free beyond 120 days after treatment. CPT-11 clearly retained its anti-tumor activity at a lower dosage (27 mg kg-1 day-1). CPT-11 was significantly more active than cyclophosphamide, thiotepa and etoposide against the 3 xenografts evaluated. To study the schedule dependency of its anti-tumor activity, CPT-11 was given i.v. at the same total doses over the same period (33 days) using either a protracted or a sequential schedule in IGRM34-bearing mice. With a dose of 10 mg kg-1 day-1 given on days 0-4, days 7-11, days 21-25 and days 28-32 (total dose, 200 mg kg-1), 3 of 6 animals were tumor free on day 378. The same total dose given with a sequential schedule, i.e., 20 mg kg-1 day-1 on days 0-4 and days 28-32, failed to induce complete regression. The plasma pharmacokinetics of CPT-11 and SN-38 (active metabolite of CPT-11) were studied in IGRM34-bearing animals after a single i.v. dose of 10 and 40 mg kg-1. The plasma

clearance rate of CPT-11 was dose dependent. The ratio between the SN-38 and CPT-11 area under the curve in plasma was 0.4-0.65, i.e., significantly higher than that obsd. in humans at the max. tolerated dose (0.01-0.05). Conversely, this ratio was 10-fold lower in tumor than in plasma. Clin. development of irinotecan is warranted in pediatric malignancies.

Answer 25:

Bibliographic Information

Topotecan increases topoisomerase IIα levels and sensitivity to treatment with etoposide in schedule-dependent process. Whitacre, Cecilia M.; Zborowska, Elizabeth; Gordon, Nahida H.; Mackay, Wilma; Berger, Nathan A. Department of Medicine, and Cancer Center, Case Western Reserve University School of Medicine, Cleveland, OH, USA. Cancer Research (1997), 57(8), 1425-1428. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 126:325111 AN 1997:269603 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

To elucidate the effect of topoisomerase (Topo) I inhibitors in the modulation of Topo II levels and sensitivity to Topo II-directed drugs, athymic mice bearing SW480 human cancer xenografts were treated with simultaneous, subsequent, or distant doses of topotecan and etoposide. This in vivo study demonstrates that simultaneous administration of topotecan and etoposide results in an antagonistic response. In contrast, inhibition of Topo I by topotecan results in a compensatory increase in Topo IIα levels assocd. with increasing sensitivity of tumors to subsequent treatment with the Topo II inhibitor etoposide. Furthermore, we show that Topo IIα levels decline 5 days after the last dose of topotecan, resulting in restoration of the original response of the xenografts to etoposide. Thus, this study emphasizes the crit. role of schedule dependency to optimize the effectiveness of combination chemotherapy with Topo I and Topo II inhibitors.

Answer 26:

Bibliographic Information

Adding a reverser (verapamil) to combined chemotherapy overrides resistance in small cell lung cancer xenografts. Arvelo, F.; Poupon, M. F.; Bichat, F.; Grossin, F.; Bourgeois, Y.; Jacrot, M.; Bastian, G.; Le Chevalier, T. CNRS, Institut Curie, Paris, Fr. European Journal of Cancer, Part A (1995), 31A(11), 1862-8. Publisher: Elsevier, CODEN: EJCTEA Journal written in English. CAN 124:134977 AN 1996:39796 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Small cell lung carcinomas (SCLC) are characterized by chemosensitivity to diverse antitumoral compds. However, responses are transitory and relapses are commonly obsd. The authors examd. the ability of verapamil, a reverser of P-glycoprotein (Pgp)-related resistance, to improve the efficacy of CyCAV combined chemotherapy (Cy, cyclophosphamide (CPA); C, cisplatin (CDDP); A, doxorubicin (ADM);V, etoposide (VP16)), as currently administered to SCLC patients at Institute Gustave-Roussy, France, and adapted to the treatment of nude mice implanted with these tumors. Although Pgp encoded by the MDR1 (multidrug resistance) gene is not the only mechanism for multidrug resistance (MDR), and not all drugs included in this regimen are recognized by Pgp, the authors anticipated a therapeutic benefit. Four different SCLC lines, expressing the MDR1 gene and recently grafted into nude mice, were used. SCLC-75, SCLC-6 and SCLC-41 originated from untreated patients, and SCLC-74T was derived from a patient treated with a combination of ADM, CPA and VP16. SCLC-41T and SCLC-6T tumors were used after having undergone, resp., five and nine cycles of in vivo passage and CyCAV treatment of the tumor-bearing nude mice, to reinforce their chemoresistance. The efficacy of the CyCAV regimen, assocd. with or without verapamil (given 24 h before CyCAV on days 1-5), was tested on the growth of these SCLC. Verapamil (25 mg/kg) improved the antitumor effect of CyCAV in mice bearing SCLC-6T, SCLC-41T and SCLC-75 tumors, although toxicity was obsd. Verapamil modestly delayed the plasma clearance of ADM. Two daily injections of 10 mg/kg of verapamil, administered at a 3 h interval, proved to be effective, whereas the same total dose administered as a bolus was not. These results indicate that the assocn. of some reversers of MDR, including drugs possibly interacting with Pgp, might potentiate SCLC combined chemotherapy.

Answer 27:

Bibliographic Information

Anti-B4-blocked ricin synergizes with doxorubicin and etoposide on multidrug-resistant and drug-sensitive tumors. O'Connor, Rosemary; Liu, Changnian; Ferris, Cynthia A.; Guild, Braydon C.; Teicher, Beverly A.; Corvi, Christopher; Liu, Yimao; Arceci, Robert J.; Goldmacher, Victor S.; et al. Dana-Farber Cancer Inst., Boston, MA, USA. Blood (1995), 86(11), 4286-94. Publisher: Saunders, CODEN: BLOOAW ISSN: 0006-4971. Journal written in English. CAN 124:45029 AN 1995:972819 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Anti-B4-blocked ricin (anti-B4-bR) is an immunotoxin directed against CD19-pos. cells that is currently being tested in several B-cell leukemia/lymphoma clin. trials. To explore the possibility of using anti-B4-bR in combination with chemotherapy protocols, the authors investigated the in vitro and in vivo cytotoxic effects of combining it with doxorubicin or etoposide using the lymphoma cell line Namalwa and a P-glycoprotein-expressing cell line, Namalwa/mdr-1, obtained by retroviral infection of Namalwa cells with the mdr-1 gene. Namalwa/mdr-1 cells were slightly more sensitive to anti-B4-bR than Namalwa cells; IC37 values were approx. 4 pmol/L and 8 pmol/L, resp. When anti-B4-bR was combined simultaneously with doxorubicin or etoposide, additive to supra-additive killing of Namalwa and Namalwa/mdr-1 cells was obsd. In xenografts of Namalwa/mdr-1 cells in severe combined immunodeficiency (SCID) mice, doxorubicin and etoposide at their max. tolerated doses (3 mg/kg × 3 or 15 mg/kg × 3) showed no therapeutic effect. However, treatment with 5 daily bolus injections of anti-B4-bR (50 μg/kg) followed by treatment with doxorubicin or etoposide significantly increased the life span of the mice by 129% and 115%, resp. After treatment with anti-B4-bR, the Namalwa/mdr-1 population expressed lower levels of P-glycoprotein, and this decrease may account for the synergistic action of the drug combinations. These results suggest that anti-B4-bR could be used to good effect in combination with current treatment regimens and further hint at a promising role for this immunotoxin in treatment of disease at the minimal residual disease stage, where cells may be resistant to chemotherapy.

Answer 28:

Bibliographic Information

Therapeutic effect of CDDP and VP-16 against human bladder cancers. Gotoh, Akinobu; Mizuno, Yoshihito; Okada, Hiroshi; Arakawa, Soichi; Kitazawa, Sohei; Maeda, Sakan; Kamidono, Sadao. School Medicine, Kobe University, Kobe, Japan. In Vivo (1995), 9(3), 263-7. Publisher: International Institute of Anticancer Research, CODEN: IVIVE4 ISSN: 0258-851X. Journal written in English. CAN 123:306144 AN 1995:870759 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In order to evaluate the anticancer effect of combination chemotherapy (CDDP and etoposide) against human bladder cancer xenografts transplanted in nude mice, we tried an exptl. chemotherapy. The tumor was aseptically cut and s.c. transplanted into the backs of the nude mice. When the wt. of each tumor reached 300mg, CDDP (day 1; 4mg/kg) and etoposide (day 1-5; 2mg/kg) were given i.p. as single agent or in combination and repeated every 3 wk. The estd. wt. (mg) was obtained by (larger diam. X smaller diam.2) X 1/2. A continuous significant effect was obsd. in CDDP combined with etoposide against bladder tumor. Therefore, these results suggest that the combination chemotherapy using CDDP with etoposide is an efficacious treatment against human bladder cancer.

Answer 29:

Bibliographic Information

In vivo effects of recombinant human lymphotoxin on human medulloblastoma xenograft: enhancement of antitumor activity of etoposide. Mikami, Takashi; Uozumi, Tohru; Kurisu, Kaoru; Kawamoto, Keiichi; Kiya, Katsuzo; Hotta, Takuhiro. Department of

Neurosurgery, Hiroshima University School of Medicine, Hiroshima, Japan. Biotherapy (Dordrecht, Netherlands) (1995), Volume Date 1994, 8(1), 7-17. Publisher: Kluwer, CODEN: BTHREW ISSN: 0921-299X. Journal written in English. CAN 123:74390 AN 1995:679421 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The authors investigated the antitumor activities of rHuLT alone and in combination with etoposide on human medulloblastoma xenografts growing s.c. in nude mice. I.v. administration of rHuLT (1.0 × 105U/kg, 5.0 × 105U/kg, 2.5 × 106U/kg, three times a week for three weeks) suppressed medulloblastoma growth depending on the dose. However, the highest dosage caused serious side effects. Combining rHuLT (i.v., 5.0 × 105U/kg, three times a week for three weeks) with etoposide (i.p., 20mg/kg, once a week for three weeks) increased the antitumor activity without causing serious toxicity. Microscopically, tumor specimen showed thrombosed tumor vessels and massive necrosis 3 wk after rHuLT treatment. Ultrastructural examn. revealed that 120 min after the administration of rHuLT alone, disruption of inter-endothelial junctions was evident, and that the endothelial cells were destroyed at 240 min. Concn. of etoposide in tumor tissue peaked 30 min after i.p. administration, and then decreased with time. When etoposide was administered in combination with rHuLT, the concn. of etoposide in tumor tissue after 60 to 240 min was significantly higher than when etoposide was given alone, and the area under the concn. vs. time curve was also greater for the tumors of mice with combination treatment. The findings suggest that the proper combination of rHuLT and etoposide may have synergistic antitumor activities. Histol. changes suggest that increased concns. of etoposide within the tumor after combination therapy may occur due to increased vascular permeability and/or decreased etoposide clearance which is the result of blood stasis in the tumor vasculature.

Answer 30:

Bibliographic Information

In vivo assessment on the therapeutic effects of etoposide, vincristine and mitomycin C against human neuroblastoma.
Kaneko, Michio; Kaneko, Setsuko; Ohkawa, Haruo. Inst. Clin. Med., Univ. Tsukuba, Tsukuba, Japan. Gan to Kagaku Ryoho (1991), 18(7), 1155-61. CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 115:222933 AN 1991:622933 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Antitumor effects of etoposide (VP-16), vincristine and mitomycin C were evaluated with 4 human neuroblastoma xenograft, according to Battelle Columbus Labs. protocol. Etoposide is one of the agents which has been reported to be effective against advanced neuroblastoma clin., if combined with other agents. While vincristine was effective against 1 out 4 neuroblastoma xenografts, TS-N-2, with 58.1% max. inhibition rate, etoposide was assessed ineffective as a single agent in all of the 3 xenografts used. Since etoposide had no effect on the wt. gain in nude mice in this xenograft expt., the dose of etoposide was increased two-fold against 2 xenografts, but found ineffective also in the increased dose. Mitomycin C, which as not been used in childhood malignant tumors, was effective against 2 out of 4 xenografts, TNB-9 and SK-N-AS, with 72.0% and 78.4% max. inhibition rates, resp.

Answer 31:

Bibliographic Information

Studies on chemotherapy for adenocarcinoma of the uterine cervix using xenografts transplanted in nude mice.
Yamagishi, Masaji. Fac. Med., Toyama Med. Pharm. Univ., Toyama, Japan. Nippon Sanka Fujinka Gakkai Zasshi (1991), 43(2), 165-72. CODEN: NISFAY ISSN: 0300-9165. Journal written in Japanese. CAN 115:341 AN 1991:400341 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Adenocarcinoma of the human uterine cervix was successively transplanted into nude mice and the effects of chemotherapy on

adenocarcinoma of uterine cervix were investigated in this transplanted tumor. First, it was confirmed that both the original tumor and the transplanted tumor were apparently histol. the same as adenocarcinoma of the uterine cervix (endocervical type). And the transplanted tumor was shown to have the features of adenocarcinoma by an electron microscope. The doubleing time of the transplanted tumor was 9.2 days. For the chemotherapy study, first the therapeutic effects of 11 kinds of agents were screened by single-agent chemotherapy applied to the transplanted tumor. From the results of this series, 6 regimens for multi-agent chemotherapy were tried on the transplanted tumor. The effects of the chemotherapy were evaluated following Battelle Columbus Labs. Protocol and histopathol. The relative regression rates for the tumors treated with mitomycin C (MMC) + cyclophosphamide (CPM) and MMC + CPM + methotrexate (MTX) were 72.99 and 80.9% (Tn/To = 0.84), resp. The results suggest that the combinations of MMC + CPM or MMC + CPM + MTX are regimens that are possibly effective on the adenocarcinoma of human uterine cervix and are worth be trying clin.

Answer 32:

Bibliographic Information

Enhanced in vivo cytotoxicity of recombinant human tumor necrosis factor with etoposide in human renal cell carcinoma. Evaluation in a preclinical model. Donaldson, J. T.; Keane, T. E.; Poulton, S. H.; Walther, Philip J. Sch. Med., Duke Univ., Durham, NC, USA. Urological Research (1990), 18(4), 245-50. CODEN: URLRA5 ISSN: 0300-5623. Journal written in English. CAN 113:224201 AN 1990:624201 CAPLUS

Abstract

The combination of tumor necrosis factor (TNF) and etoposide (ETP) was evaluated for potential cytotoxic efficacy against a human renal cell carcinoma xenograft using an in vivo assay employing an athymic mouse host with tumor implanted a the subrenal capsule site. Both antitumor efficacy (relative survival or RTS) and toxicity (wt. loss) of TNF and ETP alone and in combination were evaluated. While TNF and ETP alone were mildly inhibitory (RTS 90% and 71%, resp.), the combination caused marked tumor inhibition (45% of controls). Host toxicity encountered with the combination did not exceed the toxicity assocd. with ETP alone, suggesting that the therapeutic index may have been augmented. It is concluded that enhanced antitumor activity without substantial augmentation of toxicity is obsd. with this combination, providing a rationale for further evaluation of tumor necrosis factor-based regimens for the treatment of advanced renal carcinoma.

Answer 33:

Bibliographic Information

An in vivo human tumor xenograft model of etoposide resistance. Rose, William C.; Basler, George A. Pharm. Res. Dev. Div., Bristol-Myers Co., Inc., Wallingford, CT, USA. In Vivo (1989), 3(4), 249-53. CODEN: IVIVE4 ISSN: 0258-851X. Journal written in English. CAN 112:30158 AN 1990:30158 CAPLUS

Abstract

HCT-116 and HCT-116/E represent human colon carcinoma lines characterized in vitro as sensitive and resistant, resp., to etoposide. Using both subrenal capsule (src) and s.c. implants, the authors sought to develop in vivo tumor models of these cell lines. Src implantation of tumor fragments into athymic mice yielded reproducible growth (165-271%) for both tumor models during the 10-day assay period. The max. therapeutic effects for etoposide on the preferred schedule (Days 1 and 5, i.p.) were (mean 78% tumor inhibition vs. src HCT-116 compared to 45% tumor inhibition vs. src HCT-116/E). The modest but significant differential sensitivity toward etoposide seen in the src tumor setting was not obsd. in the s.c. tumor models. Principally, this was due to the insensitivity of s.c. HCT-116 to etoposide, even when treatment was initiated one day post-implant. Interestingly, mitomycin C, included as a pos. ref. drug, was more active vs. s.c. HCT-116/E than s.c. HCT-116. In summary, src tumor models for etoposide sensitivity and resistance have been developed as in vivo counterparts for cell lines with characterized differential sensitivity to etoposide in vitro.

Answer 34:

Bibliographic Information

Recombinant human tumor necrosis factor alone and with chemotherapeutic agents. Effect on nude mouse-supported human bladder cancer heterografts. Das, Anurag K.; Walther, Philip J.; Buckley, Niall J.; Poulton, Susan H. M. Sch. Med., Duke Univ., Durham, NC, USA. Archives of Surgery (Chicago, IL, United States) (1989), 124(1), 107-10. CODEN: ARSUAX ISSN: 0004-0010. Journal written in English. CAN 110:112847 AN 1989:112847 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effect of recombinant human tumor necrosis factor (rhTNF) alone and in combination with cisplatin, etoposide, doxorubicin, or dactinomycin on the growth of heterotransplants of human bladder transitional cell carcinoma was studied using a modified subrenal capsule assay in athymic nude mice. Only etoposide potentiated rhTNF cytotoxicity; no increase in host toxicity was noted. Variably enhanced toxic side effects were seen with other combinations. Thus, rhTNF combined with etoposide may have potential clin. exploitable therapeutic synergism in the treatment of advanced bladder cancer.

Answer 35:

Bibliographic Information

Activity and distribution studies of etoposide and mitozolomide in vivo and in vitro against human choriocarcinoma cell lines. Brindley, Charles J.; Pedley, R. Barbara; Antoniw, Pari; Newlands, Edward S. Dep. Med. Oncol., Charing Cross Hosp., London, UK. Cancer Chemotherapy and Pharmacology (1987), 19(3), 221-5. CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 108:31488 AN 1988:31488 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The in vivo antitumor activity of etoposide and mitozolomide was assessed in nude mice bearing a xenograft (CC3) of human gestational choriocarcinoma. Both agents demonstrated, at best, marginal activity obsd. as a delay in tumor growth. This lack of sensitivity suggests that the CC3 xenograft is not a good model for selection of agents for clin. evaluation in gestational choriocarcinoma. Plasma and tissue concns. of etoposide and mitozolomide were measured in nude mice. Drug concns. found in tumor tissue were 60% and 30% of plasma levels for mitozolomide and etoposide, resp. Etoposide and mitozolomide activity was also evaluated in vitro with another choriocarcinoma cell line (JAR). Max. cell-kill was achieved after exposure to etoposide at 0.05-1 μg/mL for 3-24 h. This in vitro response to etoposide demonstrates the importance of exposure time in detg. cytotoxicity. In contrast, mitozolomide at 1-100 μg/mL did not have a marked effect against JAR after exposure for 3-24 h.

Answer 36:

Bibliographic Information

Fundamental and clinical investigations on the reinforcement of the effects of combination cancer chemotherapy by flow cytometric analysis of DNA histograms. New attempts at reinforcement of antitumor effects using FCM. Sato, Yasumitsu. Sch. Med., Akita Univ., Japan. Akita Igaku (1986), 13(4), 561-86. CODEN: AKIGDV ISSN: 0386-6106. Journal written in Japanese. CAN 107:168379 AN 1987:568379 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effects of cis-diamminedichloroplatinum (CDDP), peplomycin (PEP), mitomycin C (MMC), adriamycin (ADM), etoposide (VP-16), 5-fluorouracil (5-FU), and vindesine (VDS) upon the viability and cell cycle progression of cultured human esophageal cancer cells (TE-2, AE-2), human esophageal (AEN-2), or gastric (TK) tumor xenografts growing in nude mice were measured and compared using

flow cytometry (FCM) in order to improve the methods of selecting the individual agents and establish the most effective regimen for combination cancer chemotherapy. Anal. of the influence of chemotherapeutic agents on cell cycle kinetics using FCM appeared to be very important in the development of an effective cancer chemotherapy. Recruitment and partial synchronization were esp. useful in reinforcing the antitumor effects of combination chemotherapy on solid cancers.

Answer 37:

Bibliographic Information

Enhancement of etoposide-induced cytotoxicity by cyclosporin A. Osieka, Rainhardt; Seeber, Siegfried; Pannenbaecker, Rita; Soll, Detlef; Glatte, Peter; Schmidt, Carl Gottfried. West Ger. Cancer Cent., Innere Universitaetsklin. Poliklin., Essen, Fed. Rep. Ger. Cancer Chemotherapy and Pharmacology (1986), 18(3), 198-202. CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 106:168654 AN 1987:168654 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Following the clin. observation of enhanced antineoplastic action of etoposide [33419-42-0] in the presence of cyclosporin A (CyA) [59865-13-3], this drug interaction was investigated in several in vitro and in vivo tumor systems. Macromol. DNA damage induced by etoposide at drug levels comparable to plasma AUC (area under the concn.-time curve) values achieved in patients was increased not only in leukemic peripheral blood cells from patients but also in mononuclear peripheral blood cells from a healthy donor. Intracellular retention of radioactivity from [3H]etoposide was increased by a factor of 1.5 at the most in the presence of CyA. The cytotoxicity of etoposide and adriamycin to L 1210 leukemic cells was clearly enhanced, whereas CyA had no effect on the action of cisplatin or ionizing irradn. At CyA blood levels not exceeding 1.44 μg/mL, increased tumor inhibition of etoposide was obsd. in a human embryonal cancer xenograft, but there was also higher lethality in normal mice. With respect to chemosensitization the effects of CyA resemble those of Ca channel blockers or anticalmodulin agents. In contrast to Ca channel blockers, however, adequate plasma levels of CyA can well be achieved in patients.

Answer 38:

Bibliographic Information

Xenografts in pharmacologically immunosuppressed mice as a model to test the chemotherapeutic sensitivity of human tumors. Floersheim, G. L.; Bieri, A.; Chiodetti, Nicole. Zent. Lehre Forsch., Kantonssp., Basel, Switz. International Journal of Cancer (1986), 37(1), 109-14. CODEN: IJCNAW ISSN: 0020-7136. Journal written in English. CAN 104:81665 AN 1986:81665 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A human tumor xenograft model using pharmacol. immunosuppressed mice was assessed for its suitability to test preclinically the sensitivity of colorectal carcinomas, bone sarcomas and melanomas against anticancer agents. Beside ionizing radiation, 14 cytotoxic drugs including 5-fluorouracil (5-FU) [51-21-8], dimethylmyleran (DMM) [55-93-6], cytosine arabinoside [147-94-4], cyclophosphamide [50-18-0], melphalan [148-82-3], mitomycin C [50-07-7], adriamycin [23214-92-8], bleomycin [11056-06-7], etoposide [33419-42-0], vinblastine [865-21-4], cisplatin [15663-27-1], procarbazine [671-16-9], DTIC [4342-03-4], and BCNU [154-93-8] were assayed. Ionizing radiation, 5-FU and DMM were also applied at LDs followed by bone-marrow rescue high-dose therapy. Four colon carcinomas responded poorly to most of the agents but one tumor displayed marked sensitivity to BCNU. LDs of radiation, 5-FU and DMM and cyclophosphamide and by an osteosarcoma to the latter drug. No strong effects were seen against melanomas. LDs of DMM induced the best regression of one colon carcinoma. In general, the superiority of high-dose therapy for solid human tumors compared to maximally tolerated doses was demonstrated. Individual carcinomas of the same type displayed different drug sensitivity.

Answer 39:

Bibliographic Information

In vivo effects of recombinant human lymphotoxin on human medulloblastoma xenograft: enhancement of antitumor activity of etoposide. Mikami T; Uozumi T; Kurisu K; Kawamoto K; Kiya K; Hotta T Department of Neurosurgery, Hiroshima University School of Medicine, Japan Biotherapy (Dordrecht, Netherlands) (1994), 8(1), 7-17. Journal code: 8903031. ISSN:0921-299X. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 7547084 AN 96053655 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The authors investigated the antitumor activities of rHuLT alone and in combination with etoposide on human meduloblastoma xenografts growing subcutaneously in nude mice. Intravenous administration of rHuLT (1.0 x 10(5) U/kg, 5.0 x 10(5)U/kg, 2.5 x 10(6)U/kg, three times a week for three weeks) suppressed medulloblastoma growth depending on the dose. However, the highest dosage caused serious side effects. Combining rHuLT (intravenously, 5.0 x 10(5)U/kg, three times a week for three weeks) with etoposide (intraperitoneally, 20mg/kg, once a week for three weeks) increased the antitumor activity without causing serious toxicity. Microscopically, tumor specimen showed thrombosed tumor vessels and massive necrosis 3 weeks after rHuLT treatment. Ultrastructural examination revealed that 120 minutes after the administration of rHuLT alone, disruption of interendothelial junctions was evident, and that the endothelial cells were destroyed at 240 minutes. Concentration of etoposide in tumor tissue peaked 30 minutes after intraperitoneal administration, and then decreased with time. When etoposide was administered in combination with rHuLT, the concentration of etoposide in tumor tissue after 60 to 240 minutes was significantly higher than when etoposide was given alone, and the area under the concentration versus time curve was also greater for the tumors of mice with combination treatment. The findings suggest that the proper combination of rHuLT and etoposide may have synergistic antitumor activities. Histological changes suggest that increased concentrations of etoposide within the tumor after combination therapy may occur due to increased vascular permeability and/or decreased etoposide clearance which is the result of blood statis in the tumor vasculature.

Answer 40:

Bibliographic Information

Treatment of a human renal cell carcinoma in nude mice with recombinant human tumor necrosis factor alpha and etoposide. Hofmockel G; Bassukas I D; Heimbach D; Wirth M; Maurer-Schultze B Department of Urology, University of Wurzburg, Germany The Journal of urology (1993), 150(6), 1974-9. Journal code: 0376374. ISSN:0022-5347. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 8230548 AN 94047459 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The effect of treating a human renal cell adenocarcinoma xenografted into Balb/c-nu/nu (nude) mice with recombinant human tumor necrosis factor alpha (TNF alpha) and the cytostatic agent etoposide (ETP) as monotherapy or combination has been studied. Antitumor effects were evaluated by determining growth of the tumor implants by external caliper measurements and tumor cell proliferation by determining the labelling index (LI) after pulse labelling with 3H-thymidine. The toxicity of the treatment with TNF alpha and/or ETP was also studied by measuring the animal weight. Monotherapy with TNF alpha had no effect on tumor growth or proliferation. Treatment with ETP as a single agent, TNF alpha plus ETP applied concurrently and TNF alpha plus ETP two days later led to a slight inhibition of tumor growth and also to a slight decrease of the LI. In contrast to a monotherapy with TNF alpha, all therapeutic modalities containing ETP showed an increased toxic effect on the animals represented by a distinct weight loss. This suggests that the minute efficacy of the treatment observed could well be due solely to its toxicity. In contrast to two other studies, no additive or synergistic effect of the antineoplastic activity of TNF alpha and/or ETP was found. The intertumoral variation of human renal cell carcinomas could be one reason for the different results with this therapeutic regimen.

Answer 41:

Bibliographic Information

Phase II study: treatment of non-Hodgkin's lymphoma with an oral antitumor derivative of bis(2,6-dioxopiperazine). Ohno R; Yamada K; Hirano M; Shirakawa S; Tanaka M; Oguri T; Kodera Y; Mitomo Y; Ikeda Y; Yokomaku S; + Department of Medicine, Nagoya University School of Medicine, Branch Hospital, Japan Journal of the National Cancer Institute (1992), 84(6), 435-8. Journal code: 7503089. ISSN:0027-8874. (CLINICAL TRIAL); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 1538420 AN 92167304 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND: Although razoxane (ICRF-159), a derivative of bis(2,6-dioxopiperazine), has shown significant antitumor activity in several murine tumors, inadequate bioavailability has limited its clinical efficacy. Sobuzoxane (MST-16), another derivative of bis(2,6-dioxopiperazine), has shown activity against a broad spectrum of murine tumors and human tumor xenografts in nude mice and a lack of cross-resistance to vincristine, doxorubicin, cyclophosphamide, fluorouracil, etoposide, and mitomycin C. These findings suggest that MST-16 has a mode of cytocidal activity different from that of other antitumor agents. PURPOSE: The present late phase II study was conducted to evaluate the clinical efficacy and toxicity of MST-16 in non-Hodgkin's lymphoma (NHL). METHODS: As part of a multi-institutional cooperative study, we conducted a study of MST-16 in 27 patients with NHL who were assessable for drug efficacy and toxicity. MST-16, a bis(2,6-dioxopiperazine) analogue and an inhibitor of topoisomerase II, was administered orally at a dose of 1600 mg/m2 a day for 5-7 days at intervals of 2-3 weeks. RESULTS: Response consisted of one complete remission and seven partial remissions in 27 assessable patients. Response was achieved at a median of 13 days (range, 9-62 days) after initiation of therapy and lasted a median of 46 days (range, 29-155 days). Major toxic effects were leukopenia in 70% of the patients, thrombocytopenia in 44%, and gastrointestinal disorders in 37%. CONCLUSIONS: MST-16 was shown to be effective in NHL and deserves further clinical trial, since the drug shows little cross-resistance to available antitumor drugs. IMPLICATIONS: Phase II clinical studies of MST-16 in treatment of breast cancer, gastric cancer, and adult T-cell leukemia and lymphoma are also being conducted in Japan. Future trials of combination chemotherapy using MST-16 with other antitumor drugs are warranted in view of the additive effects observed in studies of MOLT-3 cells and studies of L1210 leukemia in mice.

Answer 42:

Bibliographic Information

Chemotherapy-radiation interactions in human cervix carcinoma xenografts. Tonkin K S; Kelland L R; Steel G G Radiotherapy Research Unit, Institute of Cancer Research, Sutton, Surrey, UK British journal of cancer (1988), 58(6), 738-41. Journal code: 0370635. ISSN:0007-0920. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 2465016 AN 89134673 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The combination of irradiation and four agents of clinical interest in the treatment of cervix carcinoma (bleomycin, etoposide, cisplatin and ifosfamide) have been investigated using two human cervix carcinoma xenografts in nude mice. As a model of clinical brachytherapy regimes, radiation was administered at a continuous low dose rate of 5 cGy min-1 to a total dose of 9 or 12 Gy. No substantial enhancement in tumour growth delay over that observed for radiation alone was observed with bleomycin, etoposide or cisplatin. Ifosfamide, however, led to substantial additional growth delay, an effect which was lost when irradiation was administered at a higher dose rate of 70 cGy min-1. As dose-rates of around 5 cGy min-1 allow greater repair of radiation damage than at the higher dose-rate without significant cell cycling or repopulation, it is possible that ifosfamide may act as an inhibitor of repair processes in this model. It would be of interest to evaluate the role of ifosfamide and brachytherapy regimes in the clinical treatment of carcinoma of the cervix.